# An experimental series investigating the factors that influence the effect of hyperinsulinaemic euglycaemia on myocardial blood flow reserve

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## Aims

The vasodilatory effects of insulin may mitigate myocardial ischaemia, thus we conducted a series of experiments under hyperinsulinaemic euglycaemic conditions to determine how insulin infusion duration, insulin dose administered and type 2 diabetes (T2DM) affect myocardial blood flow reserve (MBFR).

## Methods

MBFR was assessed using myocardial contrast echocardiography (MCE). Hyperinsulinaemic euglycaemia was induced using a fixed-dose parenteral insulin infusion with 25% dextrose titrated to maintain euglycaemia. Three experiments were conducted between January 2016 and June 2017.

### Experiment one

Insulin duration (n=12). Participants received a 1.5 mU/kg/minute insulin-dextrose infusion (ID) or saline (control) infusion for 120 minutes. MBFR was determined at four time intervals using adenosine MCE.

### Experiment two

Insulin dose (n=22). Participants received ID with one of three insulin doses (0.5, 1.5, 3.0 mU/kg/minute) over 60 minutes.

### Experiment three

Diabetes. Six participants with T2DM and five with metabolic syndrome (MS) received ID with 1.5 mU/kg/minute of insulin over 60 minutes. In experiments two and three, baseline and 60-minute MBFR's were determined using dipyridamole MCE.

## Results

### Experiment one

Insulin duration. MBFR increased with time in the ID ($\beta = +0.01$, p=0.001), and did not change in the control group.

### Experiment two

Insulin dose. Compared with baseline, 60-minute MBFR did not change in the 0.5 mU/kg/minute, increased in the 1.5 mU/kg/minute (2.42±0.39 to 3.25±0.77, p=0.002), and decreased in the 3.0mU/kg/minute (2.64±0.25 to 2.16±0.33, p=0.02) groups.

### Experiment three

Diabetes. For comparison, the 1.5 mU/kg/minute group from experiment two (n=7) was included in analysis as a healthy control. Compared with baseline, MBFR increased in MS participants (1.98±0.33 to 2.59±0.45, p=0.04). In T2DM, both baseline and ID MBFR were significantly lower than healthy participants, and MBFR increase was borderline significant (1.67±0.35 to 2.14±0.21, p=0.05).

## Conclusion

This experimental series is the first to show that insulin infusion duration, dose and presence of T2DM dictate the effect of hyperinsulinaemic euglycaemia on MBFR. These factors require consideration when developing trials to assess the effect of insulin on myocardial ischaemia. Although previous clinical trials of insulin administration in patients with acute coronary syndromes failed to demonstrate improved outcomes, their study designs focused on achieving euglycaemia and increasing myocardial glucose uptake. If taken from a vasodilator perspective, these trials contained considerable heterogeneity of insulin-dosing protocols, which may have limited the myocardial blood flow response and

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subsequent therapeutic benefit. Therefore we propose that it may be premature to disregard the potential benefit of insulin administration during myocardial ischaemia. ■

## Conflict of interest statement

The authors report no relationships that could be construed as a conflict of interest.